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Preliminary communication

One-step synthesis of 2-acetamido-1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-D-*arabino*-hex-1-enitol, a furanoid, 2-aminoglycal derivative

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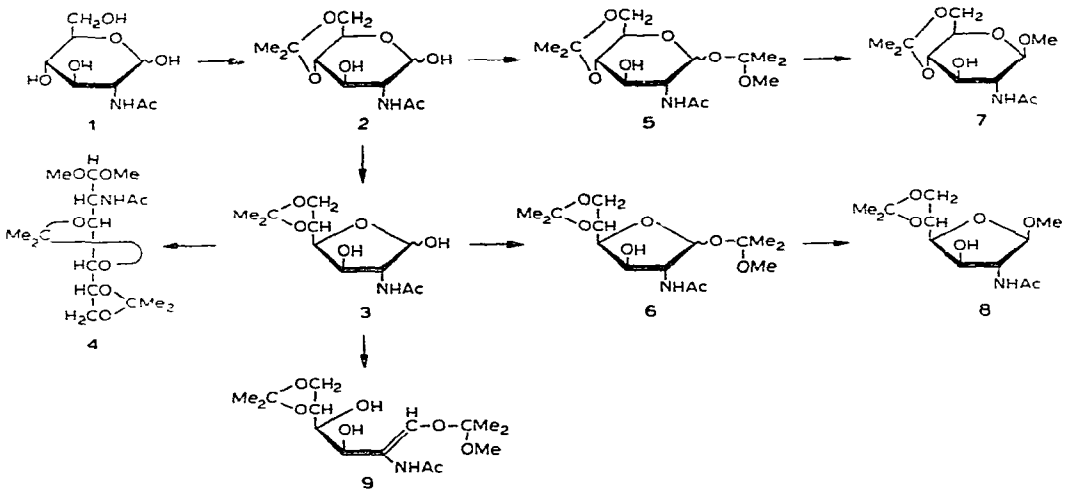
Recent work[1–4] has shown that the acetonation of *N*-substituted 2-amino-2-deoxy-D-aldohexoses with 2,2-dialkoxypropane, *N,N*-dimethylformamide, and *p*-toluenesulfonic acid at 20° gives 4,6-*O*-isopropylidene derivatives, and, at 80–90°, mainly 5,6-*O*-isopropylidenehexofuranosides in which the anomeric methoxyl or benzyloxyl group in these glycosides is *trans* to the group at C-2. In the course of our studies of the reaction mechanism, formation of a new type of glycal, a furanoid 2-aminoglycal derivative, has been observed. We report here a one-step synthesis of 2-acetamido-1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-D-*arabino*-hex-1-enitol (**10**) from 2-acetamido-2-deoxy-D-glucose (**1**), and discuss the mechanism of formation thereof.

A suspension of 2-acetamido-2-deoxy-D-glucose (**1**) (2.5 g) in dry *N,N*-dimethylformamide (50 mL) was heated at 50–55° and stirred, while 2,2-dimethoxypropane (7.5 mL) and *p*-toluenesulfonic acid monohydrate (100 mg) were added. The progress of the reaction was monitored by t.l.c.; after 15 min, the starting material was completely converted into the 4,6-*O*-isopropylidene derivative[1] (**2**). The reaction was continued for 8 h at 50–55°, and the mixture was then treated with Amberlite IR-45 ion-exchange resin to remove the acid, and evaporated *in vacuo* at 50°, to give a syrup which was chromatographed on a column of silica gel. 2-Acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-1,1-di-*O*-methyl-(D-glucose aldehydrol) (**4**) {350 mg (9%), m.p. 55–57°, $[\alpha]_D^{21}$ +5.0° (*c* 0.5, methanol); ν_{max}^{Nujol} 3280 (NH), 1650 and 1530 (amide), 1080 (ether), and 870 and 840 cm^{-1} (Me_2C); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.35 and 1.47 (3s, 12 H, 2 Me_2C), 2.02 (s, 3 H, AcN), 3.36 and 3.40 (2s, 6 H, 2 MeO), 3.5–4.7 (m, 7 H), and 5.9 (1 H, NH)}, methyl 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-β-D-glucofuranoside[2] (**8**, 950 mg, 31%), methyl 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-β-D-glucopyranoside[2] (**7**, 500 mg, 16%), 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-D-glucofuranose (**3**) {350 mg (12%), m.p. 145–147°, $[\alpha]_D^{21}$ +9° (*c* 0.85, equil., methanol); ν_{max}^{Nujol} 3360 (OH), 3300 (NH), 1620 and 1560 (amide), and 860 and 840 cm^{-1} (Me_2C); n.m.r. data at 60 MHz (in methanol-d_4): δ 1.34 and 1.40 (2s, 6 H, Me_2C), 1.97 and 2.0 (2s, 3 H, AcNα,β), 3.5–4.7 (m, 6 H, H-2–6),



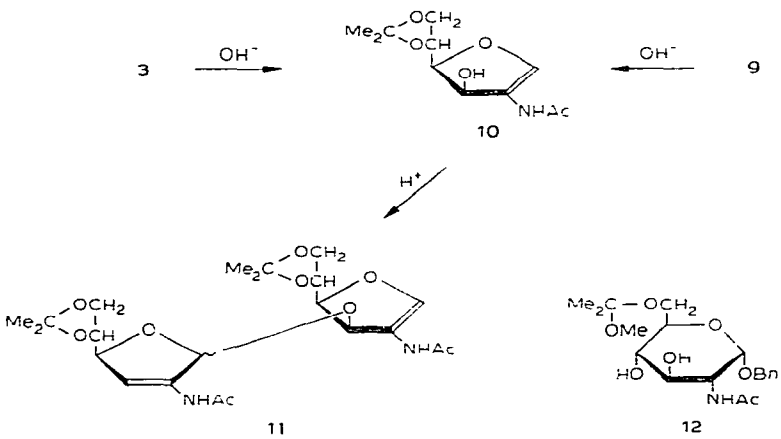
5.18 (s, H-1β), and 5.47 (d, $J_{1,2}$ 4.3 Hz, H-1α)}, 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-D-glucopyranose[1] (**2**, 360 mg, 12%), and a labile material of proposed structure[5] **9** (800 mg) were isolated.

On the other hand, the acetonation of 2-acetamido-2-deoxy-D-glucose (**1**, 2.5 g) with the reagent under the conditions just described, except that, after the reaction, the mixture was stirred for 1 h at room temperature with Amberlite IRA-410 (OH^-) ion-exchange resin (to remove the acid), instead of the Amberlite IR-45 resin used in the foregoing experiment, gave compounds **4** (350 mg, 9%), **8** (880 mg, 28%), **7** (410 mg, 13%), **2** (390 mg, 13%), and 2-acetamido-1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-D-*arabino*-hex-1-enitol (**10**) {980 mg (36%), m.p. 152°, $[\alpha]_D^{24}$ −1° (*c* 0.5, methanol); ν_{max}^{Nujol} 3200 (OH), 3140 (NH), 1670 (C=C), 1650 and 1530 (amide), and 850 cm^{-1} (Me_2C); n.m.r. data at 90 MHz (in dimethyl sulfoxide-d_6): δ 1.12 and 1.28 (2s, 6 H, Me_2C), 1.93 (s, 3 H, AcN), 3.55–4.05 (m, 3 H, H-5, 6), 4.65 (near t, 1 H, H-4), 5.68 (dd, 1 H, $J_{3,OH}$ 8.0 Hz, $J_{3,4}$ 4.0 Hz, H-3), 6.03 (s, 1 H, H-1), 6.48 (d, 1 H, $J_{3,OH}$ 8.0 Hz, 3-OH), and 9.78 (s, 1 H, NH); mass data (FD, emitter current 14 mA): *m/e* 244 $(M + 1)^+$, 243 (M^+), 222 (M^+ − Me), and 225 ($M^+ - H_2O$)}.

It is interesting that, in the latter experiment, significant amounts of the furanoid 2-aminoglycal derivative (**10**) were obtained, but none of compounds **3** and **9** was isolated. These results show that compounds **3** and **9** were converted into the furanoid 2-aminoglycal derivative (**10**) during stirring of the reaction mixture with Amberlite IRA-410 resin to remove the acid. In order to verify this conclusion, the following experiments were performed. (1) Treatment of compound **9** in methanol with Amberlite IRA-410 (OH^-) ion-exchange resin gave compound **10** in good yield, as expected. (2) A mixture of 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-D-glucofuranose (**3**, 300 mg), methanol (6 mL), and Amberlite IRA-410 resin (3 g) was stirred for 7 h at room temperature, by which time, the starting material

was no longer detectable by t.l.c.. After filtration to remove the resin, the filtrate was evaporated, to give crystalline **10** in good yield. It seems likely that the formation of furanoid 2-aminoglycals by the use of basic resins should be expected from a variety of 2-(acylamino)-2-deoxyfuranoses and their derivatives. (3) Reaction of compound **10** with alcohols in the presence of an acid catalyst gave the 2,3-unsaturated glycosides[5]. (4) Addition of a trace of *p*-toluenesulfonic acid to a solution of **10** in dry 1,4-dioxane afforded disaccharide[5] **11** quantitatively.

2,2-Dialkoxypropane–*N*,*N*-dimethylformamide–*p*-toluenesulfonic acid is a unique acetonating agent that may give unexpected, and potentially useful, products by changing such reaction conditions as temperature, reaction time, and the ratios of the acid, 2,2-dialkoxypropane, and *N*,*N*-dimethylformamide. The main route of glycoside formation may involve the attack of a methoxyl group on the acetal intermediates[6] (**5** and **6**) formed by the addition of an excess of 2,2-dimethoxypropane, and such intermediates may control the stereochemistry of the glycosides by neighboring participation of the *N*-acyl group on C-2. Recently, the acetal intermediate[6] **12** was prepared and characterized.



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